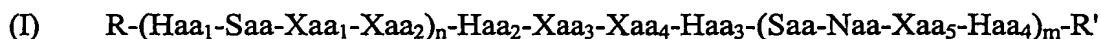


THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A conformationally constrained compound or a pharmaceutically acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):

5



wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is
10 optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

Naa is an amino acid residue with a negatively charged side chain;

Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue, Zaa₁ or Zaa₂;

15 R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

m and n are 0 or 1, provided that at least one of m and n is 1;

20 wherein a conformational constraint is provided by a linker (L) which tethers two amino acid residues, Zaa₁ and Zaa₂, in the sequence.

2. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein all of Haa₁, Haa₂, Haa₃ and Haa₄ are amino
25 acid residues with a hydrophobic side chain.

3. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Haa₁, Haa₂, Haa₃ and Haa₄ are independently selected from L-phenylalanine, L-isoleucine, L-leucine, L-valine, L-methionine and
30 L-tyrosine.

- 68 -

4. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Haa₂ is L-leucine.
5. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein each Saa is independently selected from glycine, L-alanine, L-serine, L-cysteine and aminoisobutyric acid.
6. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Naa is an L-aspartic acid or an L-glutamic acid residue.
7. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein R is an N-terminal capping group or an oligopeptide having 1 to 10 amino acid residues selected from Xaa₁, optionally capped with an N-terminal capping group.
8. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 7 wherein R is an N-terminal capping group selected from acyl and N-succinate.
9. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein R' is a C-terminal capping group or an oligopeptide having 1 to 10 amino acid residues selected from Xaa₁, optionally capped with a C-terminal capping group.
10. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 9, wherein the C-terminal capping group is NH₂.
11. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1, wherein Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are independently selected from L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-

- 69 -

cysteine, L-glutamine, L-glutamic acid, L-glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine and L-valine.

- 5 12. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein the linker (L) tethers two non-adjacent amino acids in an $i(i+7)$ relationship where the first end of the linker is attached to a first amino acid residue (Zaa_1) at a first position and the other end of the linker is attached to a second amino acid residue (Zaa_2) which is positioned 7 amino acids after Zaa_1 .
- 10 13. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein L is 4 to 8 atoms in length.
14. A conformationally constrained compound or pharmaceutically acceptable salt or
15 prodrug thereof according to claim 12 wherein Zaa_1 is located before Haa_1 at the N-terminal of the sequence and Zaa_2 is located between Haa_2 and Haa_3 .
15. A conformationally constrained compound or pharmaceutically acceptable salt or
20 prodrug thereof according to claim 12 wherein Zaa_1 is located between Haa_1 and Haa_2 and Zaa_2 is located between Haa_3 and Haa_4 .
16. A conformationally constrained compound or pharmaceutically acceptable salt or
prodrug thereof according to claim 12 wherein Zaa_1 is located between Haa_2 and Haa_3 and
25 Zaa_2 is located after Haa_4 at the C-terminal end of the amino acid sequence.
17. A conformationally constrained compound or pharmaceutically acceptable salt or
prodrug thereof according to claim 1 wherein Zaa_1 and Zaa_2 are independently selected
30 from L-aspartic acid, L-glutamic acid, L-lysine, L-ornithine, D-aspartic acid, D-glutamic acid, D-lysine, D-ornithine, L- β -homoaspartic acid, L- β -homoglutamic acid, L- β -homolysine, L- α -methylaspartic acid, L- α -methylglutamic acid, L- α -methyllysine, L- α -methylornithine, D- α -methylaspartic acid, D- α -methylglutamic acid, D- α -methyllysine

- 70 -

and L- α -methylornithine.

18. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 17 wherein Zaa₁ and Zaa₂ are independently selected
5 from L-aspartic acid, L-glutamic acid, L-lysine and L-ornithine.

19. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 18 wherein Zaa₁ and Zaa₂ are independently selected from L-aspartic acid and L-glutamic acid.

10

20. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Zaa₁ and Zaa₂ have side chains containing a carboxylic acid and the linker is selected from the group consisting of -NH(CH₂)₄NH-,
-NH(CH₂)₅NH-, -NH(CH₂)₆NH-, -NH(CH₂)₇NH-, -NH(CH₂)₂O(CH₂)₂NH-,
15 -NH(CH₂)₂N⁺H₂(CH₂)₂NH-, -NH(CH₂)₂S(CH₂)₂NH-, -NHCH₂C(=O)NH(CH₂)₂NH-,
-NH(CH₂)₂NHC(=O)CH₂NH-, -NH(CH₂)₂SS(CH₂)₂NH-, -NH(CH₂)₂O(CH₂)₃NH-,
-NH(CH₂)₂N⁺H₂(CH₂)₃NH-, -NH(CH₂)₂S(CH₂)₃NH-, -NH(CH₂)₂C(=O)NH(CH₂)₂NH-,
-NH(CH₂)₂NHC(=O)(CH₂)₂NH-, -NHCH₂C(=O)NH(CH₂)₃NH-,
-NH(CH₂)₃NHC(=O)CH₂NH-, -NHCH₂C(=O)NH(CH₂)₄NH-,
20 -NH(CH₂)₄NHC(=O)CH₂NH-, -NH(CH₂)₂C(=O)NH(CH₂)₃NH-,
-NH(CH₂)₃NHC(=O)(CH₂)₂NH-, -NH(CH₂)₃C(=O)NH(CH₂)₂NH- and
-NH(CH₂)₂NHC(=O)(CH₂)₃NH-.

21. A conformationally constrained compound or pharmaceutically acceptable salt or
25 prodrug thereof according to claim 20 wherein the linker is selected from the group consisting of -NH(CH₂)₅NH-, -NH(CH₂)₆NH-, -NH(CH₂)₇NH-,
-NHCH₂C(=O)NH(CH₂)₂NH-, -NH(CH₂)₂NHC(=O)CH₂NH-, -NH(CH₂)₂O(CH₂)₃NH- and
-NH(CH₂)₂C(=O)NH(CH₂)₂NH-.

30 22. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 20 wherein the linker is selected from the group

consisting of $\text{-NH(CH}_2)_5\text{NH-}$ and $\text{-NHCH}_2\text{C(=O)NH(CH}_2)_2\text{NH-}$.

23. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Zaa_1 and Zaa_2 have side chains containing an amino group and the linker is selected from the group consisting of
- 5 $\text{-C(=O)(CH}_2)_4\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_5\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_6\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_7\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{O(CH}_2)_2\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_2\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{S(CH}_2)_2\text{C(=O)-}$, $\text{-C(=O)CH}_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{NHC(=O)CH}_2\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{SS(CH}_2)_2\text{-C(=O)-}$,
10 $\text{-C(=O)(CH}_2)_2\text{O(CH}_2)_3\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{S(CH}_2)_3\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{NHC(=O)(CH}_2)_2\text{C(=O)-}$, $\text{-C(=O)CH}_2\text{C(=O)NH(CH}_2)_3\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_3\text{NHC(=O)CH}_2\text{C(=O)-}$, $\text{-C(=O)CH}_2\text{C(=O)NH(CH}_2)_4\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_4\text{NHC(=O)CH}_2\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{C(=O)NH(CH}_2)_3\text{C(=O)-}$,
15 $\text{-C(=O)(CH}_2)_3\text{NHC(=O)(CH}_2)_2\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_3\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$ and
 $\text{-C(=O)(CH}_2)_2\text{NHC(=O)(CH}_2)_3\text{C(=O)-}$.

24. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 23 wherein the linker is selected from the group
- 20 consisting of $\text{-C(=O)(CH}_2)_5\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_6\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_7\text{C(=O)-}$,
 $\text{-C(=O)CH}_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$, $\text{-C(=O)(CH}_2)_2\text{NHC(=O)CH}_2\text{C(=O)-}$,
 $\text{-C(=O)(CH}_2)_2\text{O(CH}_2)_3\text{C(=O)-}$ and $\text{-C(=O)(CH}_2)_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$.

25. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 23 wherein the linker is selected from the group
- 25 consisting of $\text{-C(=O)(CH}_2)_5\text{C(=O)-}$ and $\text{-C(=O)CH}_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$.

26. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Zaa_1 has a side chain containing an amino
- 30 group and Zaa_2 has a side chain containing a carboxylic acid and the linker is selected
- $\text{-C(=O)(CH}_2)_4\text{NH-}$, $\text{-C(=O)(CH}_2)_5\text{NH-}$, $\text{-C(=O)(CH}_2)_6\text{NH-}$, $\text{-C(=O)(CH}_2)_7\text{NH-}$,

- 72 -

$-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)\text{N}^+\text{H}_2(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)\text{S}(\text{CH}_2)_2\text{NH}-$,
 $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{SS}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$,
5 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_3\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_4\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_4\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_3\text{NHC}(=\text{O})(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_3\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$ and
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_3\text{NH}-$.

10

27. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 26 wherein the linker is selected from the group consisting of $-\text{C}(=\text{O})(\text{CH}_2)_5\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_6\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_7\text{NH}-$,
 $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$,
 15 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{NH}-$ and $-\text{C}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$.

20

28. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 26 wherein the linker is selected from the group consisting of $-\text{C}(=\text{O})(\text{CH}_2)_5\text{NH}-$ and $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$.

29. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 wherein Zaa₁ has a side chain containing a carboxylic acid and Zaa₂ has a side chain containing an amino group and the linker is selected from the group consisting of $-\text{NH}(\text{CH}_2)_4\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_5\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_6\text{C}(=\text{O})-$,
 25 $-\text{NH}(\text{CH}_2)_7\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)\text{N}^+\text{H}_2(\text{CH}_2)_2\text{C}(=\text{O})-$,
 $-\text{NH}(\text{CH}_2)\text{S}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})-$,
 $-\text{NH}(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_2\text{SS}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{C}(=\text{O})-$,
 $-\text{NH}(\text{CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{C}(=\text{O})-$,
 $-\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})-$,
 30 $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_3\text{NHC}(=\text{O})\text{CH}_2\text{C}(=\text{O})-$,
 $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_4\text{C}(=\text{O})-$, $-\text{NH}(\text{CH}_2)_4\text{NHC}(=\text{O})\text{CH}_2\text{C}(=\text{O})-$,

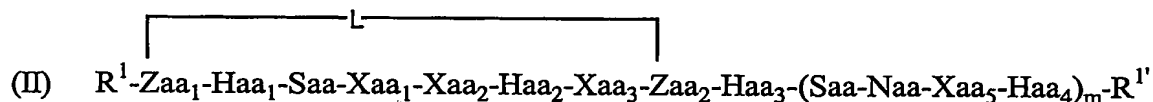
- 73 -

 $\text{-NH(CH}_2)_2\text{C(=O)NH(CH}_2)_3\text{C(=O)-,}$
 $\text{-NH(CH}_2)_3\text{NHC(=O)(CH}_2)_2\text{C(=O)-,}$
 $\text{-NH(CH}_2)_3\text{C(=O)NH(CH}_2)_2\text{C(=O)-.}$

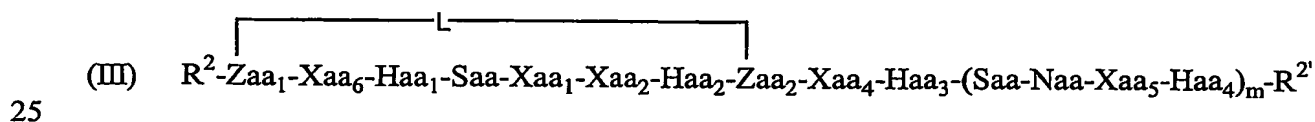
30. A conformationally constrained compound or pharmaceutically acceptable salt or
 5 prodrug thereof according to claim 29 wherein the linker is selected from the group
 consisting of $\text{-NH(CH}_2)_5\text{C(=O)-}$, $\text{-NH(CH}_2)_6\text{C(=O)-}$, $\text{-NH(CH}_2)_7\text{C(=O)-}$,
 $\text{-NHCH}_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$, $\text{-NH(CH}_2)_2\text{NHC(=O)CH}_2\text{C(=O)-}$,
 $\text{-NH(CH}_2)_2\text{O(CH}_2)_3\text{C(=O)-}$ and $\text{-NH(CH}_2)_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$.

- 10 31. A conformationally constrained compound or pharmaceutically acceptable salt or
 prodrug thereof according to claim 29 wherein the linker is selected from the group
 consisting of $\text{-NH(CH}_2)_5\text{C(=O)-}$ and $\text{-NHCH}_2\text{C(=O)NH(CH}_2)_2\text{C(=O)-}$.

32. A conformationally constrained compound or pharmaceutically acceptable salt or
 15 prodrug thereof according to claim 1, of any one of formulae (II) to (VI):

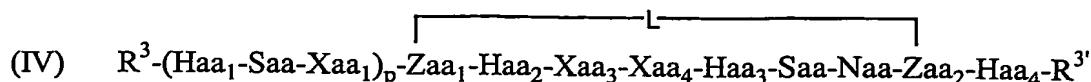


- wherein Haa₁, Haa₂, Haa₃, Haa₄, Xaa₁, Xaa₂, Xaa₃, Xaa₅, Saa, Naa and L are as
 20 defined above for formula (I), m is 0 or 1, R¹ and R^{1'} are as defined above for R and R' in
 formula (I), Zaa₁-L-Zaa₂ represents two amino acid residues with their side chains bridged
 by a linker L;

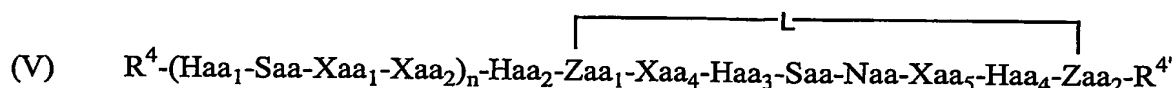


- wherein Haa₁, Haa₂, Haa₃, Haa₄, Xaa₁, Xaa₂, Xaa₄, Xaa₅, Saa, Naa and L are as
 defined above for formula (I), Xaa₆ is an amino acid residue as defined for Xaa₁ above; m
 is 0 or 1, R² and R^{2'} are as defined above for R and R' in formula (I), Zaa₁-L-Zaa₂
 30 represents two amino acid residues with their side chains bridged by a linker L;

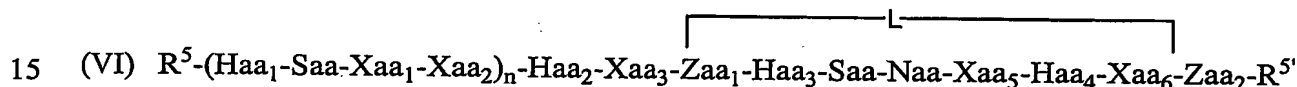
- 74 -



wherein Haa₁, Haa₂, Haa₃, Haa₄, Xaa₁, Xaa₃, Xaa₄, Saa, Naa and L are as defined above for formula (I), p is 0 or 1, R³ and R^{3'} are as defined above for R and R' in formula (I), Zaa₁-L-Zaa₂ represents two amino acid residues with their side chains bridged by a linker L;

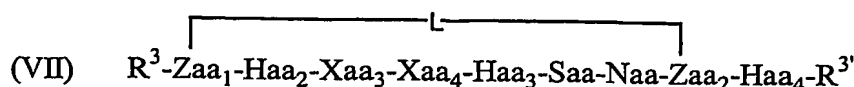


wherein Haa₁, Haa₂, Haa₃, Haa₄, Xaa₁, Xaa₂, Xaa₄, Xaa₅, Saa, Naa and L are as defined above in formula (I), n is 0 or 1, R⁴ and R^{4'} are as defined above for R and R' in formula (I), Zaa₁-L-Zaa₂ represents two amino acid residues with their side chains bridged by a linker L; and



wherein Haa₁, Haa₂, Haa₃, Haa₄, Xaa₁, Xaa₂, Xaa₃, Xaa₅, Saa, Naa and L are as defined above for formula (I), Xaa₆ is an amino acid residue as defined for Xaa₁ above; n is 0 or 1, R⁵ and R^{5'} are as defined above for R and R' in formula (I), Zaa₁-L-Zaa₂ represents two amino acid residues with their side chains bridged by a linker L; or a pharmaceutically acceptable salt or prodrug thereof.

33. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 32 having structural formula (VII):



wherein Zaa₁, Haa₂, Xaa₃, Xaa₄, Haa₃, Saa, Naa, Zaa₂, Haa₄, R³, R^{3'} and L are defined above in formula (IV).

34. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 having structural formula (VIII):



5

where Zaa₁ and Zaa₂ are selected from L-aspartic acid, L-glutamic acid; and

L is selected from -NH(CH₂)₄NH-, -NH(CH₂)₅NH-, -NH(CH₂)₆NH-, -NH(CH₂)₇NH-,
 -NH(CH₂)₂O(CH₂)₂NH-, -NH(CH₂)N⁺H₂(CH₂)₂NH-, -NH(CH₂)S(CH₂)₂NH-,
 -NHCH₂C(=O)NH(CH₂)₂NH-, -NH(CH₂)₂NHC(=O)CH₂NH-, -NH(CH₂)₂SS(CH₂)₂NH-,
 10 -NH(CH₂)₂O(CH₂)₃NH-, -NH(CH₂)₂N⁺H₂(CH₂)₃NH-, -NH(CH₂)₂S(CH₂)₃NH-,
 -NH(CH₂)₂C(=O)NH(CH₂)₂NH- and -NH(CH₂)₂NHC(=O)(CH₂)₂NH-; or

where Zaa₁ and Zaa₂ are selected from L-lysine and ornithine; and

L is selected from -C(=O)(CH₂)₄C(=O)-, -C(=O)(CH₂)₅C(=O)-, -C(=O)(CH₂)₆C(=O)-,
 -C(=O)(CH₂)₇C(=O)-, -C(=O)(CH₂)₂O(CH₂)₂C(=O)-, -C(=O)(CH₂)N⁺H₂(CH₂)₂C(=O)-,
 15 -C(=O)(CH₂)S(CH₂)₂C(=O)-, -C(=O)CH₂C(=O)NH(CH₂)₂C(=O)-,
 -C(=O)(CH₂)₂NHC(=O)CH₂C(=O)-, -C(=O)(CH₂)₂SS(CH₂)₂C(=O)-,
 -C(=O)(CH₂)₂O(CH₂)₃C(=O)-, -C(=O)(CH₂)₂N⁺H₂(CH₂)₃C(=O)-,
 -C(=O)(CH₂)₂S(CH₂)₃C(=O)-, -C(=O)(CH₂)₂C(=O)NH(CH₂)₂C(=O)- and
 -C(=O)(CH₂)₂NHC(=O)(CH₂)₂C(=O)-; or

20 where Zaa₁ is selected from L-aspartic acid, L-glutamic acid and Zaa₂ is selected from L-lysine and ornithine; and

L is selected from -NH(CH₂)₄C(=O)-, -NH(CH₂)₅C(=O)-, -NH(CH₂)₆C(=O)-,
 -NH(CH₂)₇C(=O)-, -NH(CH₂)₂O(CH₂)₂C(=O)-, -NH(CH₂)N⁺H₂(CH₂)₂C(=O)-,
 -NH(CH₂)S(CH₂)₂C(=O)-, -NHCH₂C(=O)NH(CH₂)₂C(=O)-,
 25 -NH(CH₂)₂NHC(=O)CH₂C(=O)-, -NH(CH₂)₂SS(CH₂)₂C(=O)-,
 -NH(CH₂)₂O(CH₂)₃C(=O)-, -NH(CH₂)₂N⁺H₂(CH₂)₃C(=O)-, -NH(CH₂)₂S(CH₂)₃C(=O)-,
 -NH(CH₂)₂C(=O)NH(CH₂)₂C(=O)- and -NH(CH₂)₂NHC(=O)(CH₂)₂C(=O)-; or

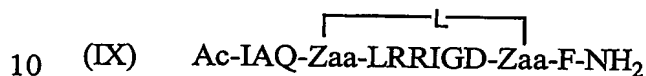
where Zaa₁ is selected from L-lysine and ornithine and Zaa₂ is selected from L-aspartic acid, L-glutamic acid; and

30 L is selected from -C(=O)(CH₂)₄NH-, -C(=O)(CH₂)₅NH-, -C(=O)(CH₂)₆NH-,

- 76 -

- $-\text{C}(=\text{O})(\text{CH}_2)_7\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)\text{N}^+\text{H}_2(\text{CH}_2)_2\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)\text{S}(\text{CH}_2)_2\text{NH}-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{SS}(\text{CH}_2)_2\text{NH}-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{NH}-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{NH}-$,
5 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$ and $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_2\text{NH}-$.

35. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 1 having structural formula (IX):



where Zaa₁ and Zaa₂ are selected from L-aspartic acid, L-glutamic acid; and

- L is selected from $-\text{NH}(\text{CH}_2)_4\text{NH}-$, $-\text{NH}(\text{CH}_2)_5\text{NH}-$, $-\text{NH}(\text{CH}_2)_6\text{NH}-$, $-\text{NH}(\text{CH}_2)_7\text{NH}-$,
 $-\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-$, $-\text{NH}(\text{CH}_2)\text{N}^+\text{H}_2(\text{CH}_2)_2\text{NH}-$, $-\text{NH}(\text{CH}_2)\text{S}(\text{CH}_2)_2\text{NH}-$,
 15 $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$, $-\text{NH}(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$, $-\text{NH}(\text{CH}_2)_2\text{SS}(\text{CH}_2)_2\text{NH}-$,
 $-\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{NH}-$, $-\text{NH}(\text{CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{NH}-$, $-\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{NH}-$,
 $-\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$, $-\text{NH}(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_2\text{NH}-$,
 $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{NH}-$, $-\text{NH}(\text{CH}_2)_3\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$,
 $-\text{NHCH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_4\text{NH}-$, $-\text{NH}(\text{CH}_2)_4\text{NHC}(=\text{O})\text{CH}_2\text{NH}-$,
 20 $-\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{NH}-$, $-\text{NH}(\text{CH}_2)_3\text{NHC}(=\text{O})(\text{CH}_2)_2\text{NH}-$,
 $-\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{NH}-$ and $-\text{NH}(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_3\text{NH}-$; or

where Zaa₁ and Zaa₂ are selected from L-lysine and ornithine; and

- L is selected from $-\text{C}(=\text{O})(\text{CH}_2)_4\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_5\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_6\text{C}(=\text{O})-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_7\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)\text{N}^+\text{H}_2(\text{CH}_2)_2\text{C}(=\text{O})-$,
 25 $-\text{C}(=\text{O})(\text{CH}_2)\text{S}(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})\text{CH}_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{SS}(\text{CH}_2)_2\text{C}(=\text{O})-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{N}^+\text{H}_2(\text{CH}_2)_3\text{C}(=\text{O})-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{C}(=\text{O})-$, $-\text{C}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{C}(=\text{O})-$,
 $-\text{C}(=\text{O})(\text{CH}_2)_2\text{NHC}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})-$,
 30 $-\text{C}(=\text{O})(\text{CH}_2)_3\text{NHC}(=\text{O})\text{CH}_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_4\text{C}(=\text{O})-$,

- 77 -

-C(=O)(CH₂)₄NHC(=O)CH₂C(=O)-, -C(=O)(CH₂)₂C(=O)NH(CH₂)₃C(=O)-,
 -C(=O)(CH₂)₃NHC(=O)(CH₂)₂C(=O)-, -C(=O)(CH₂)₃C(=O)NH(CH₂)₂C(=O)- and
 -C(=O)(CH₂)₂NHC(=O)(CH₂)₃C(=O)-; or

where Zaa₁ is selected from L-aspartic acid, L-glutamic acid and Zaa₂ is selected from

5 L-lysine and ornithine; and

L is selected from -NH(CH₂)₄C(=O)-, -NH(CH₂)₅C(=O)-, -NH(CH₂)₆C(=O)-,
 -NH(CH₂)₇C(=O)-, -NH(CH₂)₂O(CH₂)₂C(=O)-, -NH(CH₂)N⁺H₂(CH₂)₂C(=O)-,
 -NH(CH₂)S(CH₂)₂C(=O)-, -NHCH₂C(=O)NH(CH₂)₂C(=O)-,
 -NH(CH₂)₂NHC(=O)CH₂C(=O)-, -NH(CH₂)₂SS(CH₂)₂C(=O)-,
 10 -NH(CH₂)₂O(CH₂)₃C(=O)-, -NH(CH₂)₂N⁺H₂(CH₂)₃C(=O)-, -NH(CH₂)₂S(CH₂)₃C(=O)-,
 -NH(CH₂)₂C(=O)NH(CH₂)₂C(=O)-, -NH(CH₂)₂NHC(=O)(CH₂)₂C(=O)-,
 -NHCH₂C(=O)NH(CH₂)₃C(=O)-, -NH(CH₂)₃NHC(=O)CH₂C(=O)-,
 -NHCH₂C(=O)NH(CH₂)₄C(=O)-, -NH(CH₂)₄NHC(=O)CH₂C(=O)-,
 -NH(CH₂)₂C(=O)NH(CH₂)₃C(=O)-, -NH(CH₂)₃NHC(=O)(CH₂)₂C(=O)-,

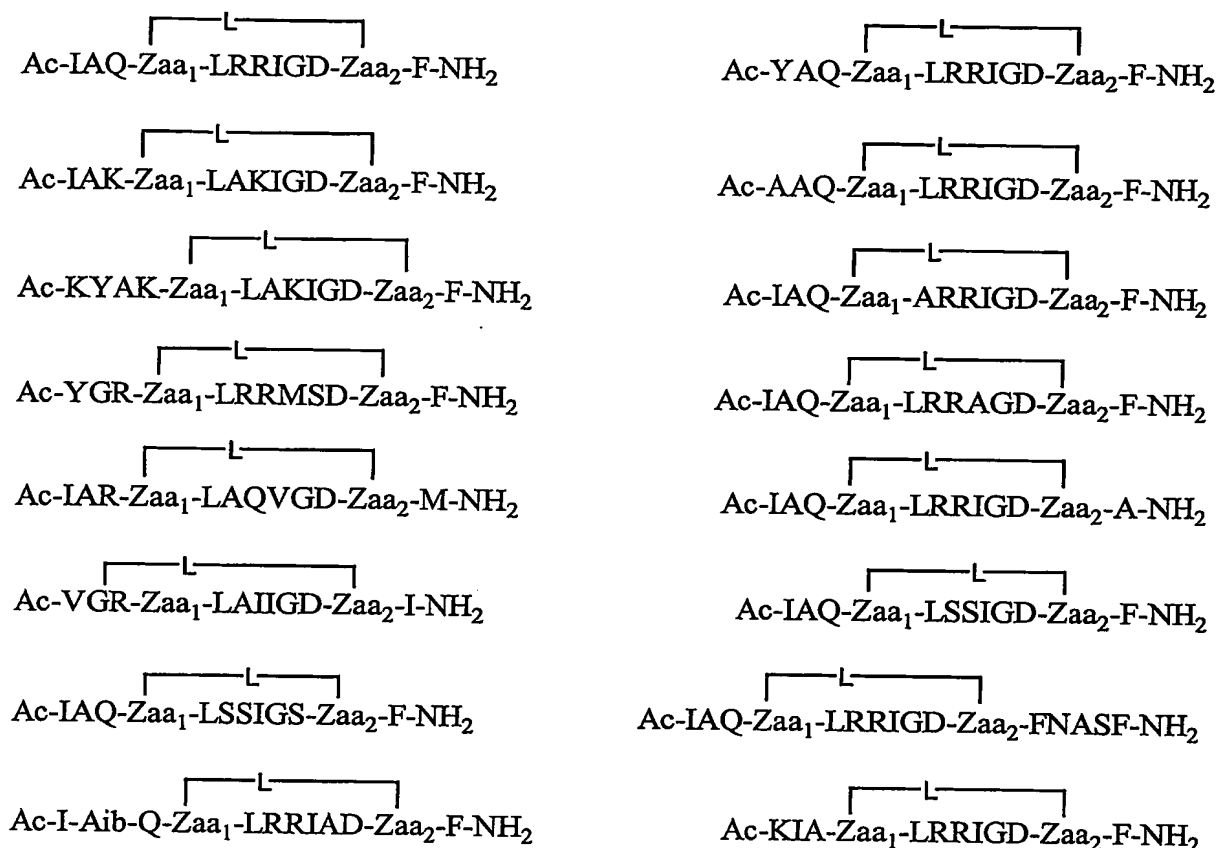
15 -NH(CH₂)₃C(=O)NH(CH₂)₂C(=O)- and -NH(CH₂)₂NHC(=O)(CH₂)₃C(=O)-; or

where Zaa₁ is selected from L-lysine and ornithine and Zaa₂ is selected from L-aspartic acid, L-glutamic acid; and

L is selected from -C(=O)(CH₂)₄NH-, -C(=O)(CH₂)₅NH-, -C(=O)(CH₂)₆NH-,
 -C(=O)(CH₂)₇NH-, -C(=O)(CH₂)₂O(CH₂)₂NH-, -C(=O)(CH₂)N⁺H₂(CH₂)₂NH-,
 20 -C(=O)(CH₂)S(CH₂)₂NH-, -C(=O)CH₂C(=O)NH(CH₂)₂NH-,
 -C(=O)(CH₂)₂NHC(=O)CH₂NH-, -C(=O)(CH₂)₂SS(CH₂)₂NH-,
 -C(=O)(CH₂)₂O(CH₂)₃NH-, -C(=O)(CH₂)₂N⁺H₂(CH₂)₃NH-, -C(=O)(CH₂)₂S(CH₂)₃NH-,
 -C(=O)(CH₂)₂C(=O)NH(CH₂)₂NH-, -C(=O)(CH₂)₂NHC(=O)(CH₂)₂NH-,
 -C(=O)CH₂C(=O)NH(CH₂)₃NH-, -C(=O)(CH₂)₃NHC(=O)CH₂NH-,
 25 -C(=O)CH₂C(=O)NH(CH₂)₄NH-, -C(=O)(CH₂)₄NHC(=O)CH₂NH-,
 -C(=O)(CH₂)₂C(=O)NH(CH₂)₃NH-, -C(=O)(CH₂)₃NHC(=O)(CH₂)₂NH-,
 -C(=O)(CH₂)₃C(=O)NH(CH₂)₂NH- and -C(=O)(CH₂)₂NHC(=O)(CH₂)₃NH-.

36. A conformationally constrained compound or pharmaceutically acceptable salt or
 30 prodrug thereof according to claim 1 selected from the group consisting of:

- 78 -



wherein Zaa₁ and Zaa₂ are as defined in claim 17 and L is a linker which tethers Zaa₁ and Zaa₂.

- 5 37. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 36 wherein Zaa₁ and Zaa₂ are independently selected from L-aspartic acid and L-glutamic acid and L is selected from the group consisting of -NH(CH₂)₅NH-, -NH(CH₂)₆NH-, -NH(CH₂)₇NH-, -NHCH₂(=O)NH(CH₂)₂NH-,
 10 -NH(CH₂)₂NHC(=O)CH₂NH-, -NH(CH₂)₂O(CH₂)₃NH- and
 -NH(CH₂)₂C(=O)NH(CH₂)₂NH-.

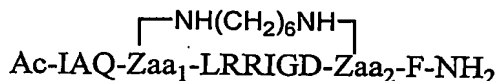
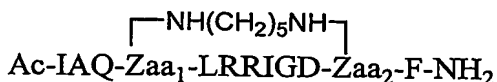
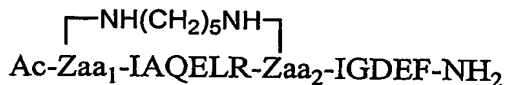
38. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 37 wherein L is selected from the group consisting of -NH(CH₂)₅NH- and -NHCH₂C(=O)NH(CH₂)₂NH-.

15

39. A conformationally constrained compound or pharmaceutically acceptable salt or

- 79 -

prodrug thereof according to claim 1 selected from the group consisting of:

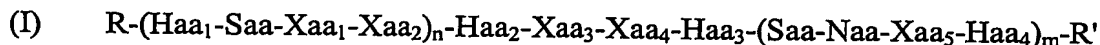


wherein Zaa₁ and Zaa₂ are independently selected from L-aspartic acid and L-glutamic acid.

5

40. A conformationally constrained compound or pharmaceutically acceptable salt or prodrug thereof according to claim 39 wherein Zaa₁ and Zaa₂ are both L-glutamic acid.

41. A pharmaceutical composition comprising a conformationally constrained compound, or a pharmaceutically acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):



15 wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

Naa is an amino acid residue with a negatively charged side chain;

20 Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue, Zaa₁ or Zaa₂;

R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

- 80 -

R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

m and n are 0 or 1, provided that at least one of m and n is 1;

wherein a conformational constraint is provided by a linker which tethers two amino acid residues, Zaa₁ and Zaa₂, in the sequence, together with one or more pharmaceutically acceptable carriers and optionally, other therapeutic and/or prophylactic ingredients.

42. An assay for identifying compounds which bind to a member of the Bcl-2 family of proteins, the assay comprising the steps of:

- 10 (a) providing a candidate compound to be tested;
- (b) contacting a Bcl-2 family protein with the candidate compound and a peptide comprising the amino acid sequence:

IAQELRRIGDEFN

15

under conditions sufficient to allow the candidate compound and the peptide to bind to the Bcl-2 family protein; and

- (c) determining whether the candidate compound has bound to the Bcl-2 family protein.

20

43. An assay according to claim 42 wherein the peptide has an amino acid sequence:

DLRPEIRIAQELRRIGDEFNETYTRR.

25

44. A method of regulating the death of a cell, comprising contacting the cell with an effective amount of a conformationally constrained compound, or a pharmaceutically acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):

30 (I) R-(Haa₁-Saa-Xaa₁-Xaa₂)_n-Haa₂-Xaa₃-Xaa₄-Haa₃-(Saa-Naa-Xaa₅-Haa₄)_m-R'

- 81 -

wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

5 Naa is an amino acid residue with a negatively charged side chain;

Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue, Zaa₁ or Zaa₂;

R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

10 R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

m and n are 0 or 1, provided that at least one of m and n is 1;

wherein a conformational constraint is provided by a linker which tethers two amino acid residues, Zaa₁ and Zaa₂, in the sequence.

15

45. A method of inducing apoptosis in unwanted or damaged cells comprising contacting said damaged or unwanted cells with an effective amount of a conformationally constrained compound, or a pharmaceutically acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):

20

(I) $R-(\text{Haa}_1\text{-Saa-Xaa}_1\text{-Xaa}_2)_n\text{-Haa}_2\text{-Xaa}_3\text{-Xaa}_4\text{-Haa}_3\text{-(Saa-Naa-Xaa}_5\text{-Haa}_4)_m\text{-R}'$

25 wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

Naa is an amino acid residue with a negatively charged side chain;

Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue, Zaa₁ or Zaa₂;

30 R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

- 82 -

R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

m and n are 0 or 1, provided that at least one of m and n is 1;

wherein a conformational constraint is provided by a linker which tethers two
5 amino acid residues, Zaa₁ and Zaa₂, in the sequence.

46. A method of treatment and/or prophylaxis of a pro-survival Bcl-2 family member-mediated disease or condition, in a mammal, comprising administering to said mammal an effective amount of a conformationally constrained compound, or a pharmaceutically
10 acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):

(I) R-(Haa₁-Saa-Xaa₁-Xaa₂)_n-Haa₂-Xaa₃-Xaa₄-Haa₃-(Saa-Naa-Xaa₅-Haa₄)_m-R'

wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue
15 with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

Naa is an amino acid residue with a negatively charged side chain;

Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue,
20 Zaa₁ or Zaa₂;

R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

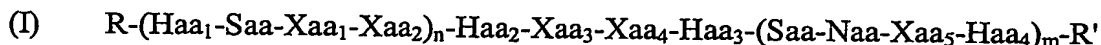
25 m and n are 0 or 1, provided that at least one of m and n is 1;

wherein a conformational constraint is provided by a linker which tethers two amino acid residues, Zaa₁ and Zaa₂, in the sequence.

47. A method according to claim 46 wherein the disease or condition is an
30 inflammatory condition, a cancer or an autoimmune disorder.

- 83 -

48. A method of treatment and/or prophylaxis of a disease or condition characterised by the inappropriate persistence or proliferation of unwanted or damaged cells in a mammal, comprising administering to said mammal an effective amount of a conformationally constrained compound, or a pharmaceutically acceptable salt or prodrug thereof, the compound comprising an amino acid sequence (I):



wherein Haa₁, Haa₂, Haa₃ and Haa₄ are each independently an amino acid residue with a hydrophobic side chain or when n and m are both 1, one of Haa₁, Haa₂ and Haa₄ is optionally Xaa₁;

each Saa is an amino acid residue with a small side chain;

Naa is an amino acid residue with a negatively charged side chain;

Xaa₁, Xaa₂, Xaa₃, Xaa₄ and Xaa₅ are each independently an amino acid residue, Zaa₁ or Zaa₂;

R is H, an N-terminal capping group or an oligopeptide optionally capped by an N-terminal capping group;

R' is H, a C-terminal capping group or an oligopeptide optionally capped by a C-terminal capping group; and

m and n are 0 or 1, provided that at least one of m and n is 1;

wherein a conformational constraint is provided by a linker which tethers two amino acid residues, Zaa₁ and Zaa₂, in the sequence.